

^{80.}
~~81.~~ (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein step (a) comprises forming a derived organism sample that consists of essentially only direct environmental organisms, step (b) comprises isolating RNA, and step (c) comprises forming a cDNA library, thereby forming a catalogued cDNA library from essentially only direct environmental organisms.

^{81.}
~~82.~~ (New) A method for forming a catalogued nucleic acid library comprising:

(a) isolating nucleic acid from a heterogeneous organism sample;

(b) subjecting all or a part of said nucleic acid sample to a selection process, and assembling all or a part of said nucleic acid sample into a nucleic acid library;

thereby forming a catalogued nucleic acid library from the heterogeneous organisms.

^{82.}
83. (New) The method of claim 82, wherein the selection process is a negative or a positive selection.

REMARKS

Claims 1-38 were pending before this response. By the present communication, claims 1-38 are cancelled without prejudice and new claims 43-83 are added to define Applicant's invention with greater particularity. These amendments add no new matter as the new claim language is fully supported by the specification and original claims. Applicant submits that the claim amendments do not narrow the claims in any way within the meaning of Festo Corporation v. Shoketsu Kinzoku Kogyo Kabushiki Co. Ltd., a/k/a SMC Corporation and SMC Pneumatics, Inc. 234 F.3d 558, 51 U.S.P.Q. 2d 1959 (Fed. Cir. 2000). Accordingly, claims 43-83 are currently pending.

The present invention provides methods for obtaining catalogued nucleic acid libraries, using techniques to increase the probability of discovery of a nucleic acid having a desirable property from an organism whose numbers may be underrepresented in an initial heterogeneous organism sample.

The Rejection Under 35 U.S.C. § 112, Second Paragraph

Applicant respectfully traverses the rejection of claims 1-38 for allegedly being indefinite under 35 U.S.C. § 112, Second Paragraph. Applicant disagrees with the Examiner's assertions with regard to claims 1-38 as follows:

With regard to the assertion that the conclusion of claim 1 does not relate back to the preamble of the claim, Applicant respectfully submits that claim 1 is cancelled without prejudice herein and replaced by new claim 43, which contains a conclusion that relates back to the preamble of the new claim.

With regard to the assertion that the phrase "a working example" does not "necessarily relate back" to the derived organism sample or the derived nucleic acid sample, Applicant respectfully submits that the term "working example" does not occur in claim 1. If the term at issue is actually "working sample," the relation between the working sample and the sample from which it is obtained is described in the Specification at page 13. However, Applicant respectfully submits that claim 1 has been cancelled and the phrase "working sample" is omitted from new claims 43-83, thus rendering moot the grounds for the rejection as to the phrase "working example."

Applicant respectfully disagrees with the Examiner's assertion that the phrase "adjusted to advantage" as used in claims 1, 6, 11 18 and 26 is unclear. Applicant respectfully submits that the Specification describes "adjusted to advantage" as a "collective term" that encompasses "selectively adjusting both the proportional representation and the population number of a constituent in a sample," which may include recovering a fraction of a sample (Spec, page 14, bottom paragraph). In addition, numerous examples of the method of "adjusting to advantage" are described, including "positive selection", "negative selection", "normalize", and "selectively enrich"-- for each of which specific definitions and examples are provided (Specification, page 15, bottom page 17, top paragraph). All of these examples involve a method wherein a portion of the sample is separated out (by any means) and then advantageously biased according to some "parameter". Further examples of such "parameters" are provided, such as "signature characteristics", "organism markers" and "nucleic acid markers" (See Specification, pages 17-19). Thus, the Examiner's assertion that the Specification does not provide a "specific definition" of the phrase "adjusted to advantage" suggests a lack of understanding that the term "adjusted to advantage" is intended as a broad term that encompasses a variety of different ways in which the original sample can be biased.

Applicant traverses the Examiner's assertion with regard to claim 2 (and claims 4, 6, 7, 9, 11, 12, 15, 18, 20, 23, 26, 28, 30, 32-35, 37 and 38) that the phrase "wherein performing the step of (a) forming a derived organism sample is comprised of resolving" is indefinite as allegedly being in addition to steps (i) and/or (ii) in claim 1. Claim 1 is now cancelled without prejudice. Applicant respectfully submits that new claims 43-83 avoid redundant language to clarify that the recitation of step (a) in claim 44 is an example of step (a) in claim 43. Thus, as recited in the new claims "resolving heterogeneity" is one way to "advantageously adjust" a sample and can be accomplished either by subjecting the initial organism sample to a method of selection (as in step (a) (i)) or by recovering a fraction of the initial organism sample having at least one desired characteristic (as in step (a) (ii)). Thus, claim 44 further limits claim 43 and the language of all new claims 43-83 has been amended to avoid any possible confusion as to whether the recitation of step (a) in dependent claims further limits the independent claim from which it depends.

With regard to the Examiner's assertion that the phrase "the heterogeneity" in claim 2 (and in claims 4, 6, 7, 9, 11, 12, 1, 18, 20, 23, 26, 28 and 30) lacks antecedent basis, Applicant respectfully submits that the new claims avoid use of "the" prior to "heterogeneity." In addition, new claim 44 recites that the initial organism sample comprises a "heterogeneous organisms," to further clarify the relationship between the term "resolving heterogeneity" and the context of the claim as a whole. Accordingly, Applicant respectfully submits that the rejection for lack of antecedent basis is now moot.

Applicant traverses the Examiner's assertion that the specification and the context of the claims provides no means for those of skill in the art to determine what is embraced by the term "resolving the heterogeneity" in claim 2 (and in claims 4, 6, 7, 9, 11, 12, 15, 18, 20, 23, 26, 28, and 30). The claims at issue are now cancelled. Accordingly, Applicant respectfully submits that the rejection involving the phrase "resolving the heterogeneity" is now rendered moot.

Applicant traverses the Examiner's assertion that the phrase "selectively enriched" in claim 4 (and in claims 9, 15, 23 and 30) lacks definition in the Specification and is further confusing in relation to the phrase "resolved heterogeneity" (Office Action, page 4). The claims at issue are now cancelled and replaced by new claims. The Specification teaches: "To 'selectively enrich' (or 'enrich' for short) a sample refers to subjecting the sample to a method such that the proportional representation of at least one component or group of components is resultantly enhanced" (Specification, page 17, top paragraph). Applicant respectfully submits that, based on this teaching in the Specification and the context of the claim as a whole, those of skill in the art would fully understand that one way in which heterogeneity of a sample can be reduced is by selectively enhancing the proportional representation of at least one component or group of components in a sample. In addition, the specification includes support for the phrase "resolving heterogeneity", for example on page 21, under "Panel D" and page 25, first complete paragraph and throughout the specification, including original claims 2 and 6. Accordingly, Applicant respectfully submits that the rejection involving the phrase "resolving the heterogeneity" is now rendered moot.

In view of the above amendments and remarks, Applicant respectfully submits that new claims 43-83 meet all requirements under 35 U.S.C. § 112, Second Paragraph and reconsideration and withdrawal of the rejection are respectfully requested.

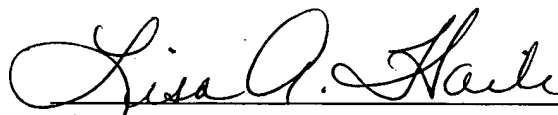
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Filed: June 3, 1998
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Attorney Docket No.: DIVER1270-3

In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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EXHIBIT A

A marked-up version of the amendments

In the claims:

Please cancel claims 1-38

Please add new claims 43-83 as follows:

-- 43. (New) A method for forming a catalogued nucleic acid library from an initial organism sample comprised of heterogeneous organisms, said method comprising:

(a) forming a derived organism sample from the initial organism sample, such that proportional representations of the constituents in said derived organism sample are adjusted to advantage by performing in any order, and at least one time, at least one step selected from the group consisting of: (i) subjecting all or a part of said initial organism sample to a method of selection, and (ii) recovering a fraction of said initial organism sample having at least one desired characteristic;

(b) isolating an initial nucleic acid sample from said derived organism sample;

(c) forming a derived nucleic acid library from said initial nucleic acid sample, such that the proportional representations of the constituents in said derived nucleic acid library are adjusted to advantage by performing in any order, and at least one time, at least one step selected from the group consisting of: (i) subjecting all or a part of said initial nucleic acid sample to a period of selection, (ii) recovering a fraction of said initial organism sample having at least one desired characteristic, and (iii) assembling all or a part of said derived nucleic acid sample into a nucleic acid library;

thereby forming a catalogued nucleic acid library from the heterogeneous organisms.

44. (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein step (a) comprises resolving heterogeneity of the initial organism sample according to at least one organism marker such that the derived organism sample is normalized with respect to organisms exhibiting the at least one organism marker.

45. (New) The method of forming a catalogued nucleic acid library according to claim 44 wherein the at least one organism marker is 16S rRNA content or 18S rRNA content of organisms in the derived organism sample.

46. (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein step (a) comprises resolving heterogeneity of said initial organism sample according to at least one organism marker such that the derived organism sample is selectively enriched with respect to organisms exhibiting the at least one organism marker.

47. (New) The method of forming a catalogued nucleic acid library according to claim 46 wherein the organisms in the derived organism sample exhibit increased 16S rRNA content or 18S rRNA content compared to those in the initial organism sample.

48. (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein step (a) comprises resolving heterogeneity of said initial organism sample according to at least two organism markers such that the derived organism sample is normalized with respect to organisms exhibiting the at least two organism markers.

49. (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein step (c) comprises resolving heterogeneity of said initial nucleic acid sample according to at least one nucleic acid marker such that the derived nucleic acid library is normalized with respect to nucleic acids exhibiting the at least one organism marker.

50. (New) The method of forming a catalogued nucleic acid library according to claim 49 wherein the at least one nucleic acid marker is G+C content of the nucleic acids in the derived nucleic acid library.

51. (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein step (c) comprises resolving heterogeneity of the initial nucleic acid sample according to at least one nucleic acid marker such that the derived nucleic acid library is selectively enriched with respect to nucleic acids exhibiting the at least one nucleic acid marker.

52. (New) The method of forming a catalogued nucleic acid library according to claim 51 wherein the at least one nucleic acid marker is G+C content of the nucleic acids in the derived nucleic acid library.

53. (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein step (c) comprises resolving heterogeneity of said initial nucleic acid sample according to at least two nucleic acid markers such that the derived nucleic acid library is advantageously adjusted with respect to nucleic acids exhibiting each of said at least two organism markers.

54. (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein step (a) comprises resolving heterogeneity of the initial organism sample according to at least one organism marker such that the derived organism sample is normalized with respect to organisms exhibiting said at least one organism marker, and also wherein step (c) comprises resolving heterogeneity of the initial nucleic acid sample according to at least one nucleic acid marker such that the derived nucleic acid library is normalized with respect to nucleic acids exhibiting the at least one nucleic acid marker.

55. (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein the at least one organism marker is 16S rRNA content or 18S rRNA content of organisms in the derived organism sample.

56. (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein the at least one nucleic acid marker is G+C content of the nucleic acids in the derived nucleic acid library.

57. (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein step (a) comprises resolving heterogeneity of said initial organism sample according to at least one organism marker such that the derived organism sample is normalized with respect to organisms that exhibit the at least one organism marker, and also wherein step (c) comprises resolving heterogeneity of the initial nucleic acid sample according to at least one nucleic acid marker such that the derived nucleic acid library is selectively enriched with respect to nucleic acids that exhibit the at least one nucleic acid marker.

58. (New) The method of forming a catalogued nucleic acid library according to claim 59 wherein the at least one organism marker is 16S rRNA content or 18S rRNA content of organisms in the derived organism sample.

59. (New) The method of forming a catalogued nucleic acid library according to claim 57 wherein the at least one nucleic acid marker is G+C content of the nucleic acids in the derived nucleic acid library.

60. (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein step (a) comprises resolving heterogeneity of said initial organism sample according to at least one organism marker such that the derived organism sample is normalized with respect to organisms exhibiting the at least one organism marker, and also wherein step (c) comprises resolving heterogeneity of said initial nucleic acid sample according to at least two nucleic acid markers such that the derived nucleic acid library is advantageously adjusted with respect to nucleic acids exhibiting each of said at least two nucleic acid markers.

61. (New) The method of forming a catalogued nucleic acid library according to claim 60 wherein said at least one organism marker is 16S rRNA content or 18S rRNA content of nucleic acids in the derived nucleic acid library.

62. (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein step (a) comprises resolving heterogeneity of said initial organism sample according to at least one organism marker such that the derived organism sample is selectively enriched with respect to organisms exhibiting the at least one organism marker, and also wherein step (c) comprises resolving heterogeneity of said initial nucleic acid sample according to at least one nucleic acid marker such that the derived nucleic acid library is normalized with respect to nucleic acids that exhibit the at least one nucleic acid marker.

64. (New) The method of forming a catalogued nucleic acid library according to claim 62 wherein the at least one organism marker is 16S rRNA content or 18S rRNA content of organisms in the derived organism sample.

65. (New) The method of forming a catalogued nucleic acid library according to claim 64 wherein the at least one nucleic acid marker is G+C content of nucleic acids in the derived nucleic acid library.

66. (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein step (a) comprises resolving heterogeneity of said initial organism sample according to at least one organism marker such that the derived organism sample is selectively enriched with respect to organisms exhibiting the at least one organism marker, and also wherein step (c) comprises resolving heterogeneity of said initial nucleic acid sample according to at least one nucleic acid marker such that the derived nucleic acid library is selectively enriched with respect to nucleic acids that exhibit the at least one nucleic acid marker.

67. (New) The method of forming a catalogued nucleic acid library according to claim 66 wherein the at least one organism marker is 16S rRNA content or 18S rRNA content of organisms in the derived organism sample.

68. The method of forming a catalogued nucleic acid library according to claim 68 wherein the at least one nucleic acid marker is G+C content of nucleic acids in the derived nucleic acid library.

69. (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein step (a) comprises resolving heterogeneity of said initial organism sample according to at least one organism marker such that the derived organism sample is selectively enriched with respect to organisms that exhibit the at least one organism marker, and also wherein step (c) comprises resolving heterogeneity of said initial nucleic acid sample according to at least two nucleic acid markers such that the derived nucleic acid library is advantageously adjusted with respect nucleic acids that exhibit each of said at least two nucleic acid markers.

70. (New) The method of forming a catalogued nucleic acid library according to claim 71 wherein the at least one organism marker is 16S rRNA content or 18S rRNA content of nucleic acids in the derived nucleic acid library.

71. (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein step (a) comprises resolving heterogeneity of said initial organism sample according to at least two organism markers such that the derived organism sample is advantageously adjusted with respect to organisms that exhibit each of said at least two organism markers, and also wherein step (c) comprises resolving heterogeneity of said initial nucleic acid sample according to at least one nucleic acid marker such that the derived nucleic acid library is normalized with respect to nucleic acids that exhibit that at least one nucleic acid marker.

72. (New) The method of forming a catalogued nucleic acid library according to claim 71 wherein the at least one nucleic acid marker is the G+C content of nucleic acids in the derived nucleic acid library.

73. (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein step (a) comprises resolving heterogeneity of said initial organism sample according to at least two organism markers such that the derived organism sample is advantageously adjusted with respect to organisms exhibiting each of said at least two organism markers, and also wherein step (c) comprises resolving heterogeneity of said initial nucleic acid sample according to at least one nucleic acid marker such that the derived nucleic acid library is selectively enriched with respect to nucleic acids that exhibit the at least one nucleic acid marker.

74. (New) The method of forming a catalogued nucleic acid library according to claim 73 wherein the at least one nucleic acid marker is G+C content of the nucleic acids in the derived nucleic acid library.

75. (New) The method of forming a catalogued nucleic acid library according to any of claims 43-74 wherein step (b) comprises isolating genomic DNA from the derived organism sample, and wherein step (c) comprises forming a genomic DNA library, thereby forming a catalogued genomic DNA library.

76. (New) The method of forming a nucleic acid DNA library according to any of claims 43-74 wherein step (b) comprises isolating genomic gene cluster DNA from the derived organism sample, and wherein step (c) comprises forming a genomic gene cluster DNA library, thereby forming a catalogued genomic gene cluster DNA library.

77. (New) The method of forming a catalogued nucleic acid library according to any of claims 43-74 wherein step (b) comprises isolating RNA from the derived organism sample, and wherein step (c) comprises forming a cDNA library, thereby forming a catalogued cDNA library.

78. (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein step (a) comprises forming a derived organism sample that consists of essentially only direct environmental organisms, thereby forming a catalogued nucleic acid library from essentially only direct environmental organisms.

79. (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein step (a) comprises forming a derived organism sample that consists of essentially only direct environmental organisms, and wherein step (b) comprises isolating genomic DNA from the derived organism sample, and also wherein step (c) comprises forming a genomic DNA library, thereby forming a catalogued genomic DNA library from essentially only direct environmental organisms.

80. (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein step (a) comprises forming a derived organism sample that consists of essentially only direct environmental organisms, and wherein step (b) comprises isolating genomic gene cluster DNA from the derived organism sample, and also wherein step (c) comprises forming a genomic gene cluster DNA library, thereby forming a catalogued genomic gene cluster DNA library from essentially only direct environmental organisms.

82. (New) The method of forming a catalogued nucleic acid library according to claim 43 wherein step (a) comprises forming a derived organism sample that consists of essentially only direct environmental organisms, step (b) comprises isolating RNA, and step (c) comprises forming a cDNA library, thereby forming a catalogued cDNA library from essentially only direct environmental organisms.

82. (New) A method for forming a catalogued nucleic acid library comprising:

(a) isolating nucleic acid from a heterogeneous organism sample;

(b) subjecting all or a part of said nucleic acid sample to a selection process, and assembling all or a part of said nucleic acid sample into a nucleic acid library;

thereby forming a catalogued nucleic acid library from the heterogeneous organisms.

83. (New) The method of claim 82, wherein the selection process is a negative or a positive selection. --